Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Augmented neutralisation resistance of emerging omicron subvariants BA.2.12.1, BA.4, and BA.5

The SARS-CoV-2 omicron (B.1.1.529) variant is highly resistant against antibody-mediated neutralisation due to many mutations in the spike (S) protein.[1] Several omicron subvariants have been detected, with BA.2.12.1 (first detected in the USA) and BA.4 and BA.5 (first detected in South Africa) currently outcompeting the previously circulating BA.1 and BA.2 subvariants in several countries. The S proteins of BA.4 and BA.5, which are identical on the protein level, and BA.2.12.1 harbour unique mutations (appendix pp 1–2), but it is largely unknown whether they differ from BA.1 and BA.2 regarding neutralisation sensitivity.

We analysed neutralisation of BA.2.12.1 and BA.4/BA.5 by monoclonal antibodies and antibodies induced on vaccination or infection, making use of S-protein-bearing reporter viruses, which represent an adequate surrogate model.[2] As a reference, we used particles bearing the S proteins of either B.1 (circulating during the early phase of the pandemic), BA.1, or BA.2. We identified that all omicron subvariants robustly evaded neutralisation by six of ten antibodies, although subvariant-specific differences were noted (appendix pp 1–2). Sotrovimab, which was reported to effectively neutralise BA.1,[1,3] showed markedly reduced neutralisation of BA.2, BA.2.12.1, and BA.4/BA.5 in comparison to neutralisation of BA.1 (appendix pp 1–2). Conversely, cilgavimab showed substantial activity against all omicron subvariants except BA.1. These results are in line with those of Cao and colleagues,[4] whereas Yamasoba and colleagues[5] reported a significant reduction of BA.4/BA.5 neutralisation by cilgavimab in comparison with neutralisation of BA.1. S2H97 showed similar efficacy against all subvariants but required high concentrations for efficient neutralisation. Finally, bebtelovimab (LY-CoV1404) neutralised all subvariants tested with similarly high efficacy (appendix pp 1–2), in agreement with findings reported for BA.1 and BA.2.[6]

We next analysed neutralisation of BA.2.12.1 and BA.4/BA.5 by plasma from ten unvaccinated people in Germany (aged 20–71 years; five male and five female) who had mild infections in March–May, 2022, when BA.1 and, subsequently, BA.2 were circulating in Germany (appendix pp 3–4). BA.1 was neutralised with 2·9-times higher efficiency (measured by the fold difference in 50% neutralisation titre values between plasma pairs) than was B.1, whereas neutralisation of BA.2 was 27·2-times more efficient than of B.1 (appendix pp 1–2), suggesting that most donors were infected with BA.2. Notably, neutralisation of BA.2.12.1 was similar to that of BA.2, whereas BA.4/BA.5 neutralisation was markedly reduced compared with BA.2 and BA.2.12.1 (ie, only 1·6-times higher than B.1; appendix pp 1–2).

We further analysed neutralisation by antibodies induced by vaccination (appendix pp 3–4). We identified that BA.1 and BA.2 evaded neutralisation by antibodies that were induced on triple BNT162b2 (Pfizer-BioNTech) vaccination with similar efficiency (ie, 4·3-times reduced neutralisation for BA.1 and 4·2-times reduced neutralisation for BA.2 compared with B.1), as expected,[7] whereas evasion by BA.2.12.1 (ie, 6·1-times reduced neutralisation compared with B.1) and particularly BA.4/BA.5 (ie, 8·1-times reduced neutralisation compared with B.1) was more efficient (appendix pp 1–2). A similar tendency was also observed for samples taken from individuals who had been triple vaccinated with BNT162b2 with subsequent BA.1 or BA.2 breakthrough infection (appendix pp 1–4).

Here, we show that bebtelovimab should represent an effective treatment for patients with COVID-19, irrespective of the infecting omicron subvariant, in keeping with bebtelovimab recognising a highly conserved epitope.[8] Further, our findings indicate that immune evasion of BA.2.12.1 is only moderately increased relative to BA.2, suggesting that increased human-to-human transmissibility (eg, due to increased replication in the upper respiratory tract or augmented infection of cells) might contribute to the expansion of BA.2.12.1. Finally, the robust neutralisation evasion by BA.4 and BA.5 indicates that these are immune-evasion variants, which are more adept than BA.1 or BA.2 to spread in populations that are vaccinated or recovering from omicron, or both.

Lancet Infect Dis 2022
Published **Online** June 28, 2022
https://doi.org/10.1016/S1473-3099(22)00422-4

See **Online** for appendix

AK, IN, SP, and MH conduct contract research (ie, testing of vaccinee sera for neutralising activity against SARS-CoV-2) for an industrial entity, unrelated to this Correspondence. GMNB served as an adviser for Moderna, unrelated to this Correspondence. All other authors declare no competing interests. SP acknowledges funding by Bundesministerium für Bildung und Forschung (01KI2006D, 01KI20328A, 01KX2021), the Ministry for Science and Culture of Lower Saxony (14–76103–184, MWK HZI COVID-19), and the German Research Foundation (PO 716/11–1, PO 716/14–1). H-MJ received funding from BMBF (01KI2043, NaFoUniMedCovid19-COVIM: 01KX2021), Bavarian State Ministry for Science and the Arts, and Deutsche Forschungsgemeinschaft through the research training groups RTG1660 and TRR130, the Bayerische Forschungsstiftung (Project CORAd), and the Kastner Foundation. GMNB acknowledges funding by German Center for Infection Research (grant no 80018019238) and a European Regional Development Fund (Defeat Corona, ZW7–8515131).

*Prerna Arora, Amy Kempf, Inga Nehlmeier, Sebastian R Schulz, Anne Cossmann, Metodi V Stankov, Hans-Martin Jäck, Georg M N Behrens, Stefan Pöhlmann, *Markus Hoffmann*
mhoffmann@dpz.eu

Infection Biology Unit, German Primate Center, 37077 Göttingen, Germany (PA, AK, IN, SP, MH) Faculty of Biology and Psychology, Georg-August-University Göttingen, Göttingen, Germany (PA, AK, IN, SP, MH); Division of Molecular Immunology, Department of Internal Medicine 3, Friedrich-Alexander University of Erlangen-Nürnberg,

Erlangen, Germany (SRS, H-MJ); Department for Rheumatology and Immunology, Hannover Medical School, Hannover, Germany (AC, MVS, GMNB); German Centre for Infection Research, partner site Hannover-Braunschweig, Hannover, Germany (MVS, GMNB)

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